PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43*bis*.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/IL2006/001059	11.09.2006	12.09.2005

International Patent Classification (IPC) or both national classification and IPC
INV. C07K16/28 A61K39/395 A61P37/00 A61P29/00 C12N15/13

Applicant
RAPPAPORT FAMILY INSTITUTE FOR RESEARCH ...

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☒ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notifed the International Bureau under Rule 66.1*bis*(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:	Date of completion of this opinion	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	see form PCT/ISA/210	Bayer, Annette Telephone No. +49 89 2399-7103

Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1 (b)).

2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

   a. type of material:

      ☒ a sequence listing

      ☐ table(s) related to the sequence listing

   b. format of material:

      ☒ on paper

      ☒ in electronic form

   c. time of filing/furnishing:

      ☒ contained in the international application as filed.

      ☒ filed together with the international application in electronic form.

      ☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

Box No. II Priority

1. ☒ The validity of the priority claim has not been considered because the International Searching Authority does not have in its possession a copy of the earlier application whose priority has been claimed or, where required, a translation of that earlier application. This opinion has nevertheless been established on the assumption that the relevant date (Rules 43*bis*.1 and 64.1) is the claimed priority date.

2. ☐ This opinion has been established as if no priority had been claimed due to the fact that the priority claim has been found invalid (Rules 43*bis*.1 and 64.1). Thus for the purposes of this opinion, the international filing date indicated above is considered to be the relevant date.

3. Additional observations, if necessary:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of

☐ the entire international application

☒ claims Nos. 5 (regarding IA)

because:

☒ the said international application, or the said claims Nos. 5 (regarding IA) relate to the following subject matter which does not require an international search *(specify)*:

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed *(specify)*:

☐ no international search report has been established for the whole application or for said claims Nos.

☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:

- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13*ter*.1(a) or (b).

☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See Supplemental Box for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-8
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-8
Industrial applicability (IA)	Yes:	Claims	1-4,6-8
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Claim 5 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item V

1. Reference is made to the following documents:

   D1: WO 2004/080385 A2 (RAPPAPORT FAMILY INST FOR RES [IL]; KARIN NATHAN [IL]) 23 September 2004 (2004-09-23) cited in the application

   D2: RUDIKOFF S ET AL: "Single amino acid substitution altering antigen-binding specificity" PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, DC, US, vol. 79, no. 6, March 1982 (1982-03), pages 1979-1983, XP002986051 ISSN: 0027-8424

   As far as not otherwise indicated, reference is made to the passages cited in the international search report.

2. Novelty

   The present application meets the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8 is new in the sense of Article 33(2) PCT:

   None of the prior art, represented by the documents cited above, discloses the polypeptides and their use as claimed by the present application.

3. Inventive step

   However, the present application does not meet the criteria of Article 33(1) PCT, because the subject-matter of claims 1-8 does not involve an inventive step in the sense of Article 33(3) PCT:

3.1 Present claims 1-4 relate to antibodies, the encoding polynucleotides and their use in a pharmaceutical composition wherein the antibody specifically binds to a human scavenger receptor.

Document D1 teaches the generation of monoclonal antibodies specifically binding human scavenger receptors like SR-B1 to be used in pharmaceutical compositions or for diagnosis. Thus taking D1 as the closest prior art document, the problem underlying the present claims 1-4 is the provision of an alternative antibody specifically binding a human scavenger receptor, the solution being an antibody as presented in claims 1 or 2.

However, an antibody against a known protein represents the outcome of routine experimentation that does not involve inventive skill.

Accordingly, present claims 1-4 are not considered as inventive.

Present claims 5-8 relate to the use of the antibodies for the treatment of inflammatory disorders.

Document D1 teaches the use of such antibodies for the treatment of inflammatory diseases like IBD, multiple sclerosis and autoimmune disease. D1 even discloses a monoclonal IgG1 antibody 5D8 having an anti-inflammatory effect. Thus, taking D1 as the closest prior art the problem to be solved may therefore be considered as to provide an antibody to be used in the manufacture of a medicament and for the treatment, the solution being an antibody for the treatment of an inflammatory disease.

The subject-matter of present claims 5-8 cannot be considered as inventive since D1 not only teaches the identical method for the generation of therapeutic monoclonal antibodies against SR-B1 as disclosed in the present application (see example 6 of D1 and example 1 of the present application) but also teaches the use of such antibodies for the claimed treatment purposes (see, e.g. page 58 lines 19-27 of D1).

Accordingly, present claims 5-8 are not considered as inventive.

3.2 Present claims 1 and 2 are drawn to a polypeptide comprising an antigen recognition domain which comprises at least three CDRs selected from SEQ-ID NOs: 11, 15, 19, 23, 27 and 31 (claim 1) or comprising all six CDRs (SEQ-ID NOs: 11, 15, 19, 23, 27, 31; claim 2) wherein the polypeptide is capable of specifically binding a human scavenger receptor.

The present application, however discloses only one antibody (E12) that specifically binds SR-B1 comprising all six CDRs, three from the VH domain (SEQ-ID NOs: 23, 27, 31) and three from the VL domain (SEQ-ID NOs: 11, 15, 19; see the examples).

It is well established in the art that the formation of an intact antigen-binding site of VH-VL paired antibodies, i.e. murine and human antibodies requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs or hypervariable regions, which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity. It is expected that all of the heavy and light chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. In this respect, it has to be pointed out that the application does not provide any guidance or direction to one skilled in the art to make and use single domain antibodies from the only disclosed antibody in the application, i.e. E12 which is a VH-VL paired antibody, as presumable meant by the present claim 1.

Furthermore, even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by document D2.
D2 teaches that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function. Thus, D2 illustrates the unpredictability in the art as far as alterations in the residues of a CDR and the effect on binding are concerned.

Accordingly, it is unlikely that antibodies that do not contain all of SEQ-ID NOs: 11, 15, 19, 23, 27 and 31 have the required function and thus solve the problem of the present application, i.e. an antibody specifically binding a human scavenger receptor (Article 33(3) PCT).

4. Additionally, the present application fails to provide sufficient evidence that would lead the skilled person to predict the ability of producing antibodies comprising fewer than all six CDRs (11, 15, 19, 23, 27 and 31) wherein all of such antibodies specifically bind a human scavenger receptor.
Accordingly, the applicant has not provided sufficient guidance to enable the skilled person to make and use the claimed antibodies (claim 1) in a manner reasonable correlated with the scope of the claims. Undue experimentation would be required to produce the invention commensurate with the scope of the claims from the written disclosure alone (Article 5 PCT).

5. For the assessment of the present claim 5 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.